Sleep Disorders

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Andreas Warnke and Christoph Wewetzer

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A. Warnke, MD (✉)
Department of Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy, University of Würzburg, Füchsleinstr. 15, 97080 Würzburg, Germany
e-mail: warnke@kjp.uni-wuerzburg.de

C. Wewetzer, MD
Department of Child and Adolescent Psychiatry and Psychotherapy, Kliniken der Stadt Köln gGmbH, Florentine-Eichler-Str. 1, 51067 Köln, Germany
e-mail: wewetzerc@kliniken-koeln.de

26.1 Definition, Classification, and Target Symptoms

Sleep disorders are characterized by difficulties with the initiation and maintenance of sleep. Duration, quality, and timing of sleep are abnormal, causing distress (insomnias, dyssomnias). There are also abnormal experiences and behaviors that occur during sleep and are regarded as disturbing by the affected person or by those around them (parasomnias).

Insomnia disorders have been categorized in various ways in different sleep disorder classification systems. The International Classification of Sleep Disorders, 2nd edition (ICSD-2), identifies insomnia as one of eight major categories of sleep disorders (American Academy of Sleep Medicine 2005) and, within this group, lists 12 specific insomnia disorders (Fig. 26.1).

ICSD-2 delineates both general diagnostic criteria that apply to all insomnia disorders, as well as more specific criteria for each diagnosis. Insomnia complaints may also occur in association with comorbid disorders or other sleep disorder categories, such as sleep-related breathing disorders, circadian rhythm sleep disorders, and

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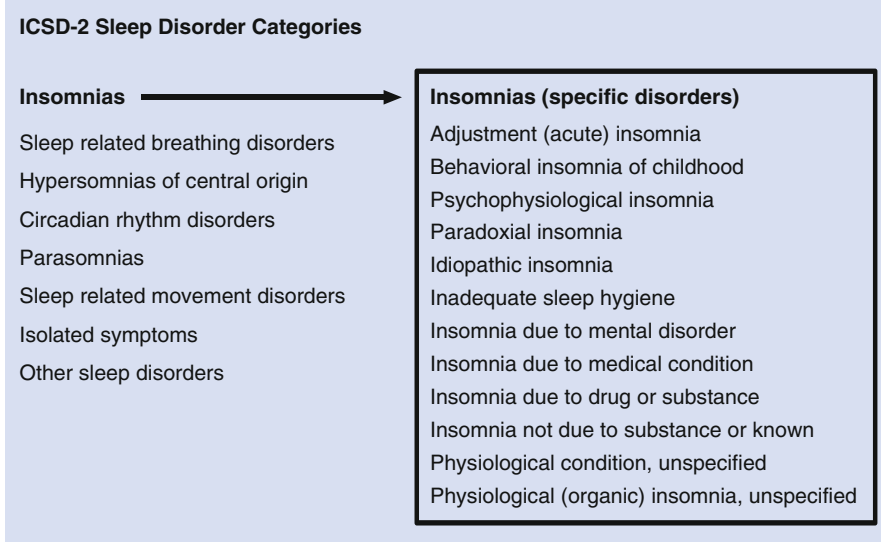

Fig. 26.1 ICSD-2 (International Classification of Sleep Disorders, 2nd Edition) insomnia diagnosis (Schutte-Rodin et al. 2008)

sleep-related movement disorders (Fig. 26.1). According to ICSD-2, an insomnia disorder is defined as a subjective report of difficulty with sleep initiation, duration, consolidation, or quality that occurs despite adequate opportunity for sleep and that result in some form of daytime impairment (Table 26.1).

Discussion is **limited** in this chapter to the sleep disorders categorized by the International Classification of Diseases, 10th revision (**ICD-10**; World Health Organization 1996), as "nonorganic sleep disorders (F51)." This excludes sleep disorders arising from primary organic disorders and those explained by misuse of psychotropic substances or medications. Nonorganic sleep disorders are diagnosed as distinct disorders if the symptoms caused by the sleep disorder predominate, even where they are symptoms of other mental or physical disorders. The **nonorganic sleep disorders** include according to ICD-10:

- Nonorganic insomnia (F51.0; DSM-5: insomnia disorder 780.52)
- Nonorganic hypersomnia (F51.1; DSM-5: hypersomnolence disorder 780.54)
- Nonorganic disorder of the sleep-wake schedule (F51.2)
- Sleep walking (somnambulism, F51.3; DSM-5: sleep walking type 307.46)

Table 26.1 Diagnostic criteria for insomnia

- A complaint of difficulty initiating sleep, difficulty maintaining sleep, or waking up too early or sleep that is chronically non-restorative or poor in quality
- The above sleep difficulty occurs despite adequate opportunity and circumstances for sleep
- At least one of the following forms of daytime impairment related to the nighttime sleep difficulty is reported by the patient:
  1. Fatigue or malaise
  2. Attention, concentration, or memory impairment
  3. Social or vocational dysfunction or poor school performance
  4. Mood disturbance or irritability
  5. Daytime sleepiness
  6. Motivation, energy, or initiative reduction
  7. Proneness for errors/accidents at work or while driving
  8. Tension, headaches, or gastrointestinal symptoms in response to sleep loss
  9. Concerns or worries about sleep

According to the American Academy of Sleep Medicine (2005)

- Sleep terrors (night terrors, pavor nocturnus, F51.4; DSM-5: sleep terror type 307.46 of "non-rapid eye movement sleep arousal disorders")
- Nightmares (F51.5; DSM-5: nightmare disorder 307.47)

In the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (**DSM-5**), sleep disorders are classified under "sleep-wake disorders" (American Psychiatric Association 2013). The classification refers partially to the ICD-10 medical conditions classification (nonpsychiatric listings) G47 (sleep disorders), partially to the F51 classification, and also to the ICSD-2. The intention is that the classification should be useful for general mental health as well as for medical clinicians. The differential diagnosis would necessitate a multidimensional approach because of possibly co-occurring nonorganic mental, medical, and neurological conditions. The chapter on "sleep-wake disorders" in DSM-5 includes ten "disorder groups": insomnia disorder (corresponding to nonorganic insomnia F51.0), hypersomnolence disorder (F51.2), narcolepsy (G47.4), breathing-related sleep disorders, circadian rhythm sleep-wake disorders, non-rapid eye movement (NREM) sleep arousal disorders (sleep walking F 51.3, sleep terrors F51.4), nightmare disorder (F51.5), rapid eye movement (REM) sleep behavior disorder, restless legs syndrome, and substance-/medication-induced sleep disorder. Associated daytime distress and impairment are core features of all these disorder groups.

The **target symptoms** depend upon the type of sleep disorder. We refer to the nonorganic sleep disorders with regard to ICD-10 (F51). These are:

- in nonorganic insomnia, disturbance of sleep initiation and maintenance, the disturbed sleep-wake schedule.
- In nonorganic hypersomnia, the increased need for sleep,
- in sleep terrors and sleep walking, the rarely severe impairment of daily life and the risk of harm to self or others resulting from agitation or motor activity during sleep.

For further information regarding the diagnosis and therapeutic interventions of sleep disorders in children, adolescents, and adults, the reader is referred to reviews published on these topics (Buford and Nemeroff 2012; Dahl and Harvey 2008; Olson et al. 2008; Owens and Mindell 2011; Mindell et al. 2006; Schutte-Rodin et al. 2008; Smith et al. 2011).

26.2 Therapeutic Framework

The **diagnosis** is made by interviewing the patient and their caregivers regarding:

- bedtime habits (sleep hygiene),
- the duration of and behavior during periods when the patient cannot fall asleep and during waking phases,
- total sleep duration and sleep behavior during the day,
- adverse consequences of the sleep disorder,
- the reactions of those around the patient to the sleep disorder.

For parasomnias, information regarding symptoms, frequency, duration, and ability to remember the parasomnia should be gathered. Information relevant to explaining insomnias is derived from the patient's developmental history, external disorder-relevant factors (parenting behavior, mental stressors, physical complaints), and questioning regarding psychiatric comorbidity (anxiety disorder, depression, ADHD, affective disorders, posttraumatic stress disorder, drug abuse). Clinical and pathological laboratory examination (EEG for patients with sleep terrors and sleep walking, sleep laboratory, and assessment of respiratory function in hypersomnias) and psychological testing (intelligence assessment, diagnostic tests for determination of psychiatric comorbidity) are appropriate in individual cases. The differential diagnosis must exclude thyroid gland dysfunction, pain syndromes, and respiratory disorders.

Therapeutic interventions are based upon comprehensive counseling and, where required, behavioral therapeutic and pharmacological interventions. **Counseling** includes explanation of the features of normal age-appropriate sleep, the elements of good sleep hygiene (regular bedtimes, falling asleep rituals, avoiding hunger and thirst), as well as supportive parenting (no unnecessary sleep phases during the day, no rewarding reinforcement of delayed bedtime or waking). **Behavioral therapeutic measures** are based upon extinction procedures, stimulus control (no daytime sleep, bed used only for sleeping), and in older children and adolescents on relaxation methods, cognitive techniques, and conflict- or stress-oriented psychotherapy (further details:

Dahl and Harvey 2008; Olson et al. 2008; Owens and Mindell 2011; Schutte-Rodin et al. 2008).

Indications for pharmacotherapy are provided by:

- Treatment of causal psychiatric or organic disorders
- Nonorganic insomnias
- Nonorganic hypersomnias
- Sleep terrors
- Sleep walking

Prior to **prescribing** sleep-inducing medication, the **following principles must be observed**:

- Consideration of the type of sleep disorder (the primary complaints, e.g., disorders of sleep initiation and/or maintenance, frequent awakenings, disorder of sleep-wake schedule, parasomnia).
- Consideration of the duration and severity of the sleep disorder.
- Consideration of everyday complaints and of the extent to which daytime performance might be affected by medication.
- Consideration of the age of the patient.
- Consideration of prior medication and treatment.
- Consideration of a primary psychiatric or other organic disorder, such as pervasive developmental disorder, ADHD, psychosis, depression, anxiety disorder, or suicidality, chronic pain, and blindness.
- Explanation of therapy for the patient and parents, with particular regard to time limits for medication, potential withdrawal reactions, avoidance of alcohol, and possible impairments of daily life arising from medication.
- Avoidance of high dosages (lowest possible dosage according to product information).
- Only short-term medication (days to 2 weeks), intermittent where possible.
- No abrupt withdrawal if medication has been continuous for 2 weeks.
- Avoidance of sedation extending into the day – unless such sedation is desirable (suicidality, for instance).
- Setting the exact dosage.
- Clarify to what extent a repeat treatment is from the outset indicated and feasible.
- The total amount of the prescribed medication for outpatients should not exceed what is required for 3–4 weeks' standard dosage. A further appointment should be scheduled for within 2–4 weeks.
- Consideration of contraindications.
- Exclusion of drug abuse in at-risk patients.

26.3 Choice of Pharmacotherapy

Because no medications, except chloral hydrate, are currently labeled by the US Food and Drug Administration (FDA) for the treatment of insomnia in children and adolescents, the use of these medication in practice settings appears to be based largely on clinical experience, empirical data derived from adults, or small case series of sedative-hypnotics in pediatric population (Owens and Mindell 2011). Table 26.2 summarizes FDA-approved drugs for insomnia in adults as well as dosages and elimination half-lifes.

The clinical guidelines for the evaluation and management of chronic insomnia in adults are generally appropriate also for younger adults (Schutte-Rodin et al. 2008) but not generally for children. **Most** of primary **sleep disorders** in children do **not need any medication**. If medication is believed to be potentially therapeutically beneficial in a given clinical situation (i.e., appropriately implemented behavioral interventions are not fully effective), the choice of sleep medication is dependent upon the target symptomatology and the attendant circumstances.

26.3.1 Benzodiazepines

The **first-choice** pharmacological treatment for primary insomnia is short-term use of **short- to intermediate-acting** benzodiazepines: examples

Table 26.2 US Food and Drug Administration (FDA)-approved medication for insomnia in adults

Drugs	Dose range (mg)	Elimination half-life (h)
Benzodiazepines		
Estazolam	1–2	10–24
Eszopiclone	2–3	6
Flurazepam	15–30	24–100
Lorazepam	2–4	10–20
Quazepam	7.5–15	25–41
Temazepam	7.5–30	8–15
Triazolam	0.125–0.5	1.5–5.5
Zaleplon	5–20	1
Zolpidem	5–10 (immediate release)	2.5
Zopiclone	3.75–7.5	3.5–6.5
Other anxiolytics and sedative-hypnotics		
Diphenhydramine (antihistamine)	25–100	8.5
Doxepin (tricyclic antidepressant)	1–6	8–24
Ramelteon (melatonin receptor agonist)	8	1–2.6

According to Buford and Nemeroff (2012)

are eszopiclone, temazepam, triazolam, zaleplon, and zolpidem (see Sect. 6.7 and Table 26.2). Eszopiclone and zolpidem demonstrated continued efficacy in adults without significant complications for 6 months, and in open-label studies for 12 months or longer (see Sect. 6.4.1). The benzodiazepines have positive effects on sleep latency, total sleep time, and/or waking after sleep onset. However, a single published clinical trial of zolpidem in children failed to show efficacy (Owens and Mindell 2011).

According to a **FDA black box warning**, benzodiazepines have been associated with reports of disruptive sleep-related behaviors including sleep walking and driving. Patients should be informed about the need of allowing appropriate sleep time and avoiding the combination of benzodiazepines with alcohol, other sedatives, and sleep restriction.

26.3.2 Sedating Antidepressants

Sedating antidepressants such as doxepin, mirtazapine, nefazodone, and trazodone, selective serotonin reuptake inhibitors (SSRIs), and tricyclic antidepressants are used in clinical practice to treat insomnia in adult and pediatric populations. An analysis of 2002 prescribing practices in the USA found that three of four medications prescribed for insomnia were antidepressants such as amitriptyline, mirtazapine, and trazodone (Walsh 2004). However, due to the occurrence or potentially significant adverse drug reactions (ADRs) such as daytime residual sedation, orthostatic hypotension, cardiac arrhythmias, and anticholinergic effects, these drugs **should not be used in nonpsychiatric patients**. According to the clinical guideline for the evaluation and management of chronic insomnia in adults that are reported to be generally appropriate also for younger adults (Schutte-Rodin et al. 2008), sedating low-dose antidepressants may be **considered only** when **insomnia** is accompanied **with comorbid depression** or in the case of other treatment failures. Examples of these drugs include amitriptyline, doxepin, mirtazapine, and trazodone.

26.3.3 Melatonin and Ramelteon

Melatonin, a nutritional substance and over-the-counter medication, and ramelteon, a FDA-approved (treatment of insomnia characterized by difficulty with sleep onset) melatonin receptor agonist (MT_1 and MT_2) with an entirely new mechanism of action that is different from classic hypnotics, have been reported to be potentially useful in the pediatric population (Coppola et al. 2004; Liu and Wang 2012; Smits et al. 2001, 2003).

Melatonin is a hormone endogenously produced by the pineal gland that plays a key role in the regulation of the sleep-wake cycle. The efficacy of melatonin supplementation has been tested in a large number of clinical trials. Meta-analyses have demonstrated that melatonin has small effects on sleep latency, with little effect on wake time after sleep onset or total sleep time. Therefore, it is **not recommended** in the treatment of **chronic insomnia** (Schutte-Rodin et al. 2008). However, there are studies in children and adolescents with insomnia accompanied with comorbid disorders showing efficacy (Smits et al. 2001, 2003; Stigler et al. 2006). For example, a randomized, placebo-controlled study

found that melatonin improves wake-sleep disorders in children with intellectual deficits (Coppola et al. 2004; for sleep disorders in children with intellectual disability, see Chap. 23). The results in the study of Smits et al. (2001) showed that melatonin, 5 mg administered at 6 p.m., was relatively safe to take in the short term, and significantly more effective than placebo in advancing sleep onset and increasing sleep duration in elementary school children with chronic sleep-onset insomnia. Sustained attention was not affected. Smits et al. (2003) found again that melatonin improved health status and advanced the sleep-wake rhythm in children with idiopathic chronic sleep-onset insomnia. In addition, melatonin was shown to be effective in reducing sleep latency in children with ADHD (van der Heijden et al. 2006).

26.3.4 Other Pharmacological Agents

Second-generation **antipsychotics** such as quetiapine and olanzapine are **only** suitable for patients with **comorbid insomnia**. Because of the significant ADRs, their use is not recommended in the treatment of insomnia in the general population (see Sects. 26.4.4 and 26.4.5).

Antihistamines (e.g., hydroxyzine, diphenhydramine) are widely used in pediatric psychiatric practice as a sedative in patients with insomnia (Zito et al. 2000). But according to the clinical guideline for the evaluation and management of chronic insomnia in adults, antihistamines are **not recommended** for long-term use (Schutte-Rodin et al. 2008).

26.3.5 Herbal Medicine

The most commonly employed herbal hypnotics include extracts of valerian (*V. officinalis*), *Melissa officinalis*, and hops. Numerous simple and combination preparations with differing dosages are commercially available, facilitating their frequent use. In contrast to medications, makers of herbal supplements do not have to get approval from the US FDA before putting their products on the market. They fall under a category called dietary supplements and are available as either over-the-counter drugs or dietary supplements.

The **efficacy** of phytotherapeutic preparations in sleep disorders has, however, **not** been compellingly **demonstrated** (Fernandez-San-Martin et al. 2010; Sarris et al. 2011; Smith et al. 2011). As a rule, a placebo effect of about 50 % of the patients medicated can be assumed in the medication of sleep disorders. *V. officinalis* is the only botanical with sufficient research of adequate rigor in the area of insomnia (Sarris et al. 2011). Meta-analyses and reviews by Fernandez-San-Martin et al. (2010) and Sarris et al. (2011) reveal that the evidence concerning the soporific plant medicine is quite varied and currently does not support its use in treating insomnia. For example, one of the meta-analysis which included 16 eligible randomized and controlled trials on Valeriana spp. monotherapy or in combination with other herbal medicines found that 9 out of 16 studies did not have positive outcomes in regard to improvement of sleep quality (Sarris et al. 2011). The safety profile of Valeriana spp. appears good; however, traditional pharmacopoeias caution it as a "cerebral stimulant" (see Sarris et al. 2011); thus, it may not consistently provide somnolence.

26.4 Treatment Strategy

26.4.1 Sleep Initiation and Sleep Maintenance Disorders in the First Half of the Night

Sedative-hypnotics with a short duration of action are appropriate here (Table 26.2), for example, zolpidem administered 30 min prior to bedtime (adult dose 5–10 mg/day). Estazolam is used for short-term treatment of insomnia characterized by difficulty in falling asleep, frequent nocturnal awakenings, and/or early morning awakenings. For adults, the recommended dose is 1 mg at bedtime.

26.4.2 Sleep Maintenance Disorders

Sedative-hypnotics with short or medium durations of action (Table 26.2), such as **benzodiazepines** (e.g., lorazepam) or **antihistamines** (e.g., diphenhydramine), are used in clinical practice.

Lorazepam is administered in adult insomnia due to anxiety or transient situational stress as a single daily dose of 0.5–2.5 mg, usually about half an hour before bedtime. In children, lower doses are recommended. In order to avoid a hangover effect, it should not, however, be given after 3 a.m.

When **employing benzodiazepines**, the following points should be noted:

- Sleepiness and slowness continuing into the day (hangover).
- Impairment of learning performance because of concentration difficulties.
- Sleep disturbance and anxiety as rebound phenomena during withdrawal.
- Respiratory depression as possible ADR, particularly with existing respiratory disorders.
- Paradoxical reaction, particularly in children with ADHD or intelligence deficits.
- The medication should essentially be employed only for very short periods because of the potential tolerance and dependence.

There are no specific dosing guidelines for **antihistamines** in children and adolescents with sleep disorders. Diphenhydramine is administered orally at doses of 25–50 mg two to three times a day. Doxylamine is administered orally at doses of 12.5 mg two to four times a day. Hydroxyzine is administered orally for anxiety disorders at doses of 25–75 mg, broken into two to three individual doses.

26.4.3 Sleep Disorders in Depression

When insomnia is accompanied with comorbid depression or in the case of other treatment failures, sedating low-dose antidepressants may be considered. Examples of these drugs include amitriptyline, doxepin, mirtazapine, and trazodone. If a sedating antidepressant drug is used as monotherapy for a patient with comorbid depression and insomnia, the dose should be that recommended for treatment of depression (see Chap. 4). In many cases, this dose will be higher than the typical dose used to treat insomnia alone (Schutte-Rodin et al. 2008).

26.4.4 Insomnias in Which Benzodiazepines and Antidepressants are Contraindicated

In nonpsychotic patients with insomnia, where benzodiazepines are contraindicated (dependence risk, medication misuse) or antidepressants are ineffective or contraindicated, low-potency antipsychotics are used in pediatric population. According to our experience, options include levomepromazine (15–30 mg/day) and melperone (20–75 mg/day) administered 30 min before bedtime as a single dose.

26.4.5 Insomnias in Context of a Psychosis

Where high-potency antipsychotics that have excellent antipsychotic but only minor sleep-promoting effects (such as haloperidol, risperidone, olanzapine, quetiapine) do not afford sufficient sleep in acute insomnia, the following alternatives are available (for dosages of antipsychotics, see Sect. 5.4.3): combination of high-potency antipsychotics with benzodiazepines (e.g., risperidone or olanzapine with lorazepam) or combination with low-potency antipsychotics (such as levomepromazine).

26.4.6 Mild Sleep Initiation Disorders, Rejection of Primarily Indicated Sleep-Promoting Agents, or Ancillary Measures for Behavioral Therapeutic Intervention: Phytotherapeutic Preparations

Herbal preparations are indicated for mild sleep initiation disorders without consequences for daily life, where the usually prescribed sleep-promoting medications are rejected by the patient or their parents, and as support

for psychoeducative and psychotherapeutic sleep therapy measures. The most commonly employed herbal hypnotics include extracts of valerian, *Melissa officinalis*, and hops. Numerous simple and combination preparations with differing dosages are commercially available. The alcohol content of some preparations should be noted.

26.4.7 Treatment of Disorders of the Sleep-Wake Schedule

Melatonin and ramelteon are employed for this indication. The recommended dose of ramelteon in adults is 8 mg taken within 30 min of going to bed. According to our personal clinical experiences, sleep disorders can be effectively treated with **melatonin**, particularly in cases where disturbances of the sleep-wake cycle are evident in children and in adolescents with visual or multiple handicaps (blindness, autism). In order to achieve a sleep-promoting effect, according to our own clinical experience, it is sufficient in many cases to take one to a maximum of 5 mg 30–60 min before retiring. The necessary dosage in an individual should be titrated in 1 mg increments.

26.4.8 Parasomnias

Nightmares do not require pharmaceutical therapy. Alcohol and the following medications can, however, induce nightmares: β-blockers, tricyclic antidepressants, barbiturates, and benzodiazepines. If the magnitude of the nightmare problem has a significantly negative impact on daily life, dosage reduction or a change of medication, if possible, may be appropriate in the case of medication-induced nightmares, and the patient should refrain from consuming alcohol.

26.4.9 Sleep Terrors and Sleep Walking

Pharmacological treatment should be preceded by psychoeducation, whereby the following should be considered:

- Sleep terrors do not represent a serious psychiatric or neurological disorder.
- Adequate nighttime sleep must be ensured.
- Safety measures should be undertaken to prevent the child from hurting itself during sleep terror episodes (closing of windows and doors; blocking of stairs by mesh).
- The child should be woken before the time point at which the sleep terrors normally occur.

It should be noted that **sleep terrors** can be **induced by** various **medications**, including lithium salts and desipramine. The decision as to whether dosage reduction or change of medication is required must be made on a case-by-case basis. Prior to pharmacological intervention, other possible triggers (sleep apnea, gastrointestinal reflux, cerebral seizures) should be excluded.

Medication is indicated only if there is **danger of physical injury** to the child, the family has caused significant distress by the severity and frequency of the sleep terrors, and the child suffers negative consequences in their daily life. Benzodiazepines and tricyclic antidepressants have proved helpful (Burstein and Burstein 1983; Cooper 1987; Fisher et al. 1973). Imipramine and diazepam can be recommended. Diazepam can be administered as a single dose of 6–10 mg to school-age children and adolescents before going to sleep. It should be noted, however, that sleep terrors can return after discontinuation of medication.

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